Supporting Information

Solid phase synthesis of oligoethylene glycol-functionalized quinolinecarboxamide foldamers with enhanced solubility properties

Synthèse en phase solide de foldamères quinolinecarboxamide munis de chaînes oligoéthylène glycol augmentant leur solubilité

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S1 Solubility studies

S1.1 Determination of extinction coefficient

Determination of sample concentration via NMR: Compound **8** was dissolved in d_6-DMSO at approximately 1 mM concentration, to which was added an equimolar quantity of pyridine, of volume accurately measured. The concentration of **8** could then be ascertained by comparing integrals of pyridine signals and nearby foldamer signals (Figure S1).

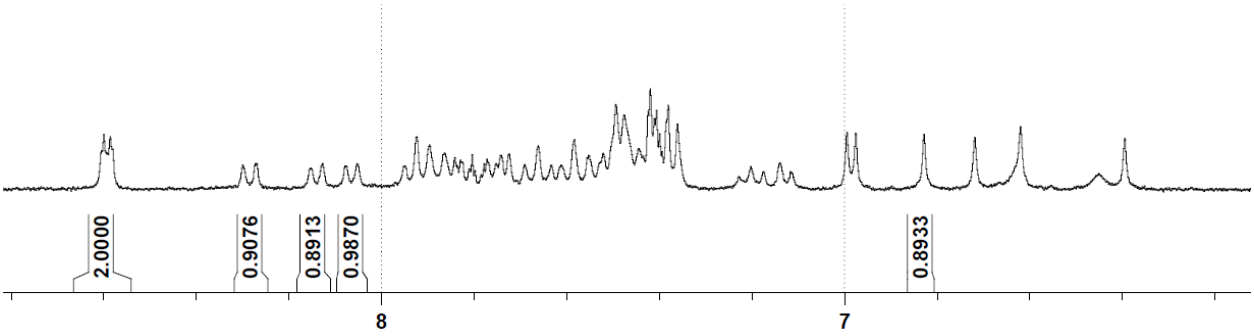


Figure S1: Expansion of ^{1}H NMR spectrum of compound **8** in d_6-DMSO containing pyridine. Integrals used are marked (pyridine 2 x CHAr δ 8.6 ppm). An average of the four foldamer signals was used to afford the concentration of **8**.

Generation of UV calibration curve: The NMR sample of **8** was then serially diluted with DMSO and UV absorbance at 375 nm measured on a NanoDrop 1000 spectrophotometer using a 1 mm pathlength. This afforded data which was used to generate a calibration curve (Figure S2), thus providing the extinction coefficient of **8** at 375 nm.

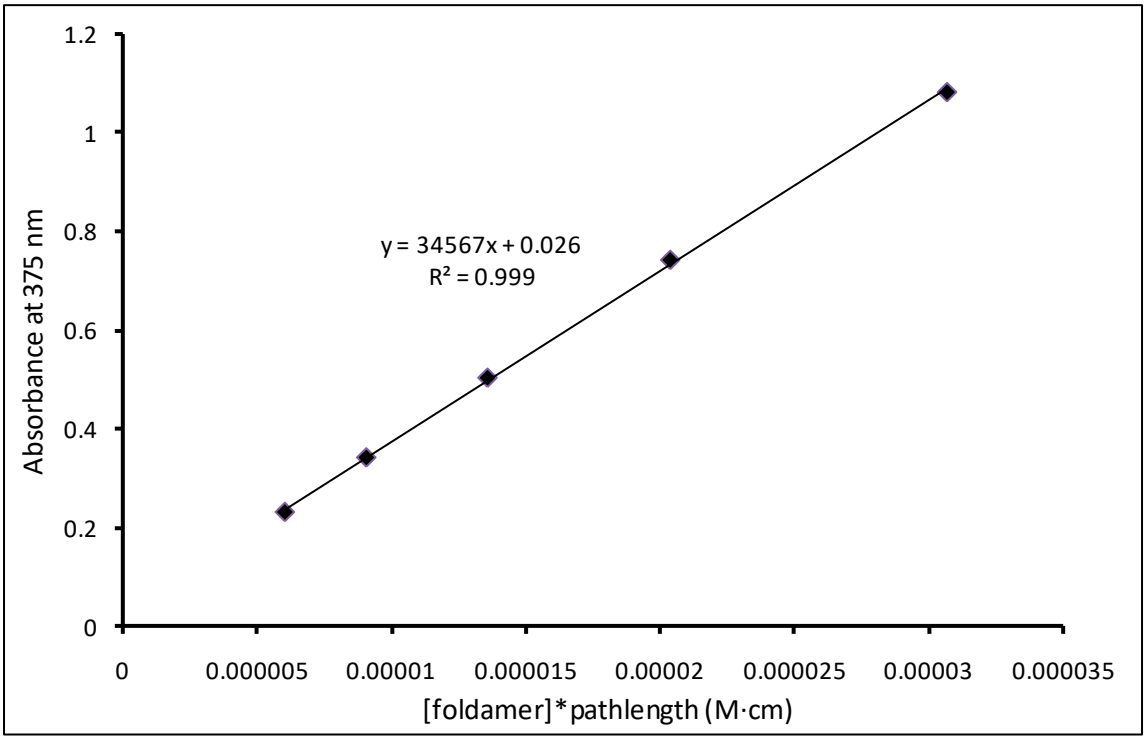


Figure S2: UV absorbance calibration curve affording the extinction coefficient of 8 at 375 nm as 34,567 $Lmol^{-1}cm^{-1}$

S1.2 Calculation of solubility

Solubility testing was carried out as described in the manuscript. The resulting samples were dissolved in spectroscopy grade DMSO and diluted to appropriate concentrations which yielded measurable absorbances at 375 nm with 1 mm pathlength. Absorbance measurements were baseline-corrected against a blank sample of spectroscopy grade DMSO. Each measurement was performed in triplicate, and the mean figure used in subsequent calculations.

S1.2.1 Compound **5**

Solvent	**Absorbance at 375 nm (1 mm pathlength)**	**[foldamer] measured (μM)**	**Dilution factor**	**[foldamer] in original sample (mM)**
n-Hexane	0.01567	4.532	0.2	0.0009064
Toluene	0.4650	134.5	1.5	0.2018
$CHCl_3$	0.6080	175.9	900	158.3
THF	0.4513	130.6	100	13.06
Isopropanol	0.05733	16.59	1	0.01659
Methanol	0.1327	38.38	1	0.03838
H_2O	0.01467	4.243	0.2	0.0008486
DMF	0.7267	210.2	100	21.02

Table S1: Absorbance measurements and calculated concentration values for compound **5**.

S1.2.2 Compound **6**

Solvent	**Absorbance at 375 nm (1 mm pathlength)**	**[foldamer] measured (µM)**	**Dilution factor**	**[foldamer] in original sample (mM)**
n-Hexane	0.009	2.603	0.2	0.0005207
Toluene	0.6427	185.9	1.5	0.2789
$CHCl_3$	0.4553	131.7	300	39.52
THF	0.8080	233.8	300	70.13
Isopropanol	0.1160	33.56	1	0.03356
Methanol	0.4433	128.3	1	0.1283
H_2O	0.03533	10.22	0.2	0.002044
DMF	0.2800	81.00	900	72.90

Table S2: Absorbance measurements and calculated concentration values for compound **6**.

S1.2.3 Compound **7**

Solvent	Absorbance at 375 nm (1 mm pathlength)	[foldamer] measured (µM)	Dilution factor	[foldamer] in original sample (mM)
n-Hexane	0.0070	2.025	0.2	0.0004050
Toluene	0.6390	184.9	300	55.46
$CHCl_3$	0.9887	286.0	300	85.80
THF	0.7437	215.1	300	64.54
Isopropanol	0.1160	33.56	1	0.03356
Methanol	0.5313	153.7	10	1.537
H_2O	0.1137	32.88	0.2	0.006577
DMF	0.4020	116.3	900	104.7

Table S3: Absorbance measurements and calculated concentration values for compound **7**.

S1.2.4 Compound **8**

Solvent	Absorbance at 375 nm (1 mm pathlength)	[foldamer] measured (µM)	Dilution factor	[foldamer] in original sample (mM)
n-Hexane	0.04967	14.37	0.2	0.002874
Toluene	0.7957	230.2	300	69.05
$CHCl_3$	0.6760	195.6	300	58.67
THF	0.9787	283.1	300	84.94
Isopropanol	0.9467	273.9	1	0.2739
Methanol	0.6953	201.2	100	20.12
H_2O	0.8570	247.9	10	2.479
DMF	0.3390	98.07	900	88.26

Table S4: Absorbance measurements and calculated concentration values for compound **8**.

S2 Chiral HPLC

Chiral HPLC was carried out as described in the Experimental Section of the manuscript.

S2.1 Compound **5**

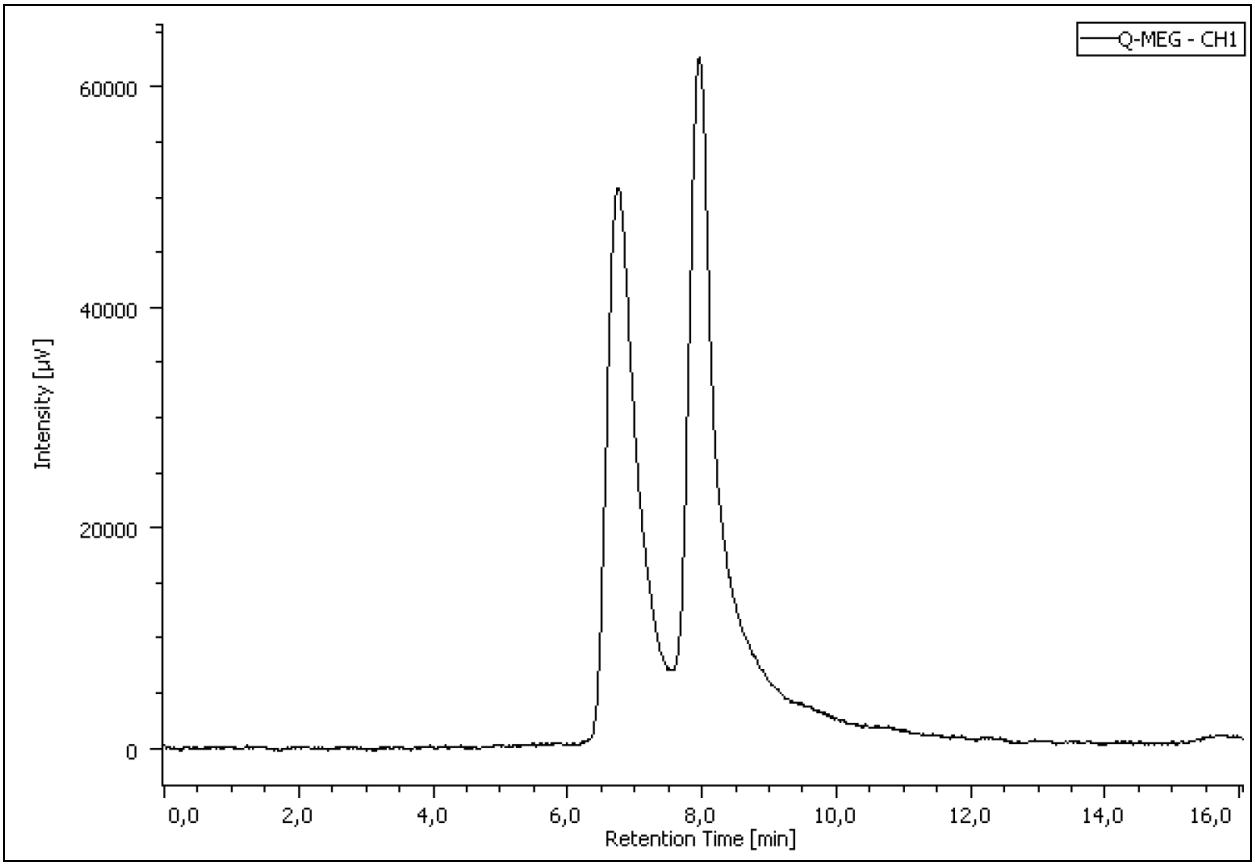


Figure S3: UV trace of compound **5** at 300 nm.

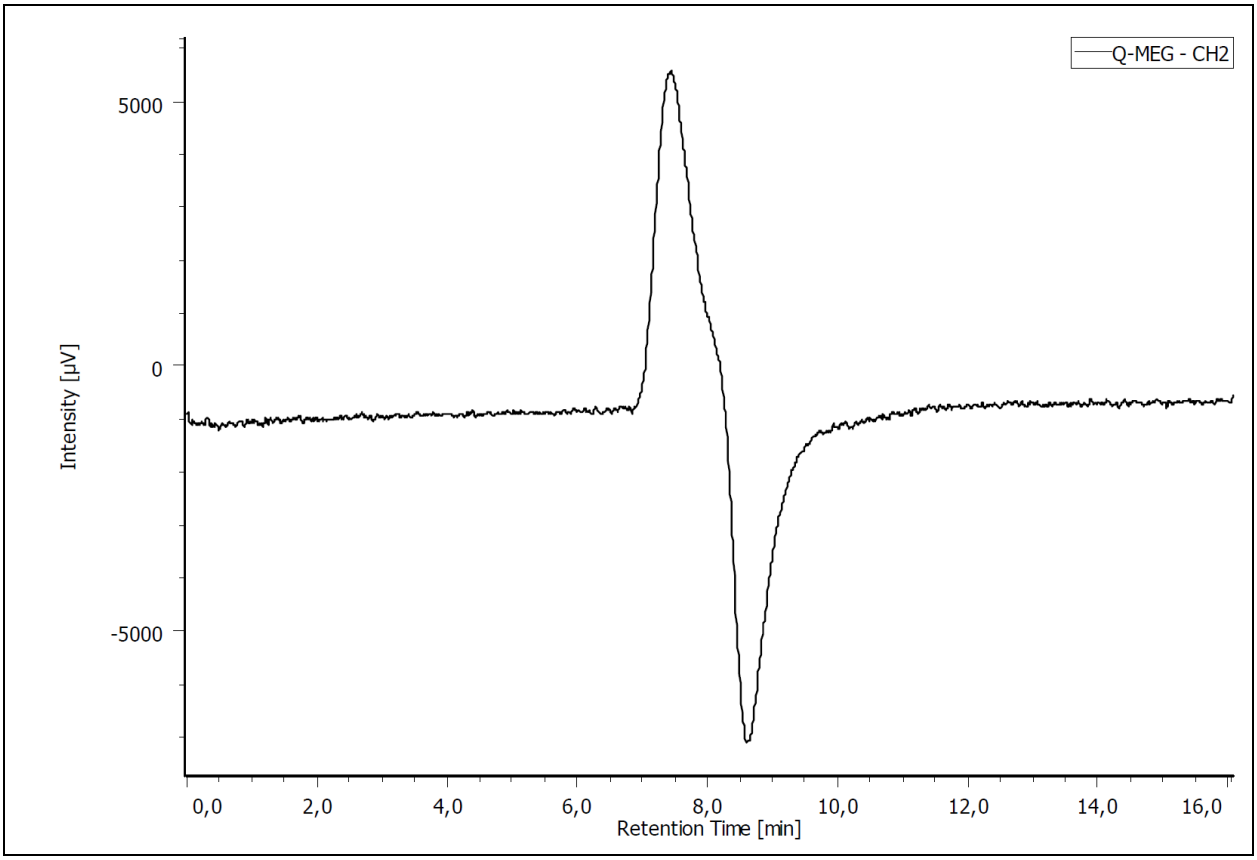


Figure S4: CD trace of compound **5** at 385 nm.

S2.2 Racemization study on M helix of compound **8**

Compound **8** was separated into P and M helices (**P-8** and **M-8**) as detailed in the manuscript. Eluted **M-8** was collected and rapidly evaporated to dryness on a vacuum line. It was then redissolved in MeOH/$CHCl_3$ (75:25) and incubated at -5 °C. Samples were then re-injected onto the chiral HPLC column at t = 5 min, then 1, 2, 4 and 8 hours after dissolution. No racemization could be detected.

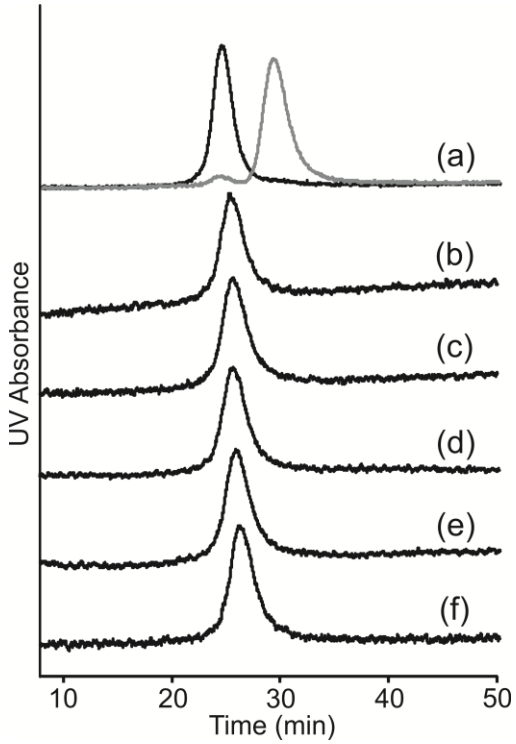
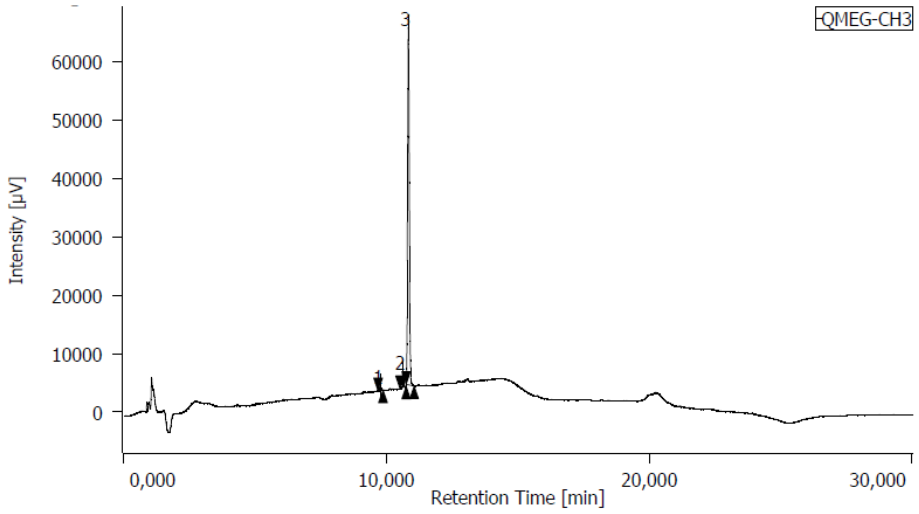


Figure S5: Expansions of: (a) Overlaid reference UV traces of separated **P-8** (grey) and **M-8** (black); Samples of **M-8** after incubation at -5 °C for: (b) 5 min; (c) 1 h; (d) 2 h; (e) 4 h; (f) 8 h.

S3 RP-HPLC data

Monomer purity was assessed by RP-HPLC prior to SPS. Analyses were performed at 1.5 mL min^{-1} using a Machery-Nagel Nucleodur C_{18} Gravity column (4.6 x 100 mm, 3 μm). The mobile phase was composed of 0.1% (v/v) TFA-H_2O (Solvent A) and 0.1% TFA-CH_3CN (Solvent B) running the following gradients: 5 – 100% B over 15 minutes (System G), 20–100% B over 20 min (System H) or 50–100% B over 22 min (System I). Monitoring by UV detection was carried out at 214 nm, 254 nm and 300 nm using a diode array detector. Foldamer purity was assessed by RP-HPLC as detailed in the Experimental section of the manuscript (Systems A, B and C).

S3.1 Compound **1**

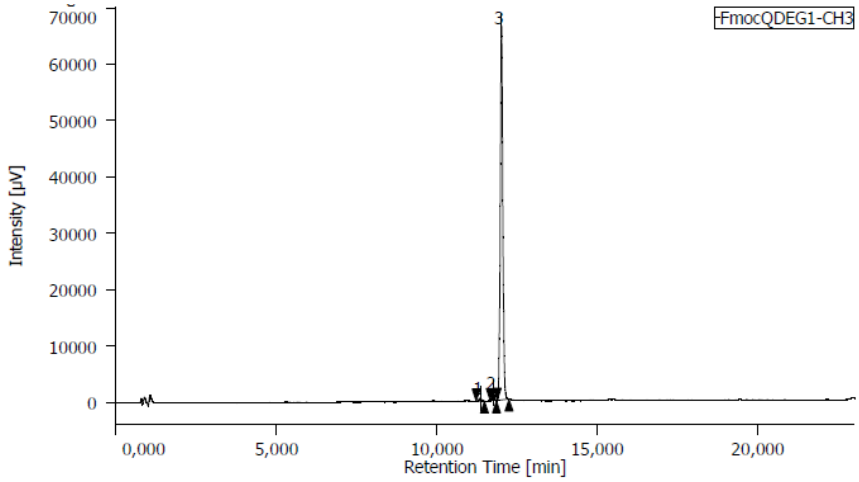


Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor
1	Unknown	3	9,783	2264	514	0,795	0,804	N/A	107748	7,375	1,085
2	Unknown	3	10,625	9104	2282	3,196	3,567	N/A	150222	1,914	1,043
3	Unknown	3	10,842	273470	61172	96,009	95,630	N/A	136615	N/A	1,123

Figure S6: Chromatogram of Compound **1** (System G, 300 nm). Purity = 96%.

S3.2 Compound **2**

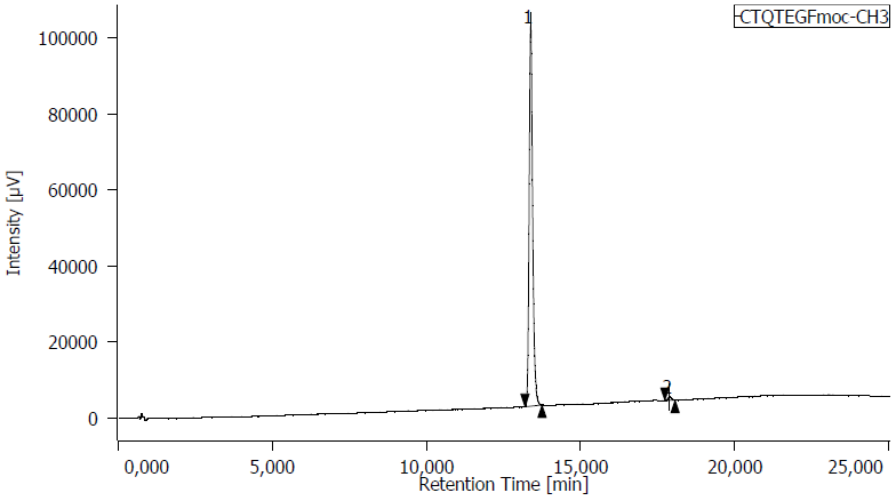


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor
1	Unknown	3	11,342	2672	498	0,698	0,729	N/A	101730	2,884	1,127
2	Unknown	3	11,750	7316	1408	1,910	2,063	N/A	109958	1,788	1,008
3	Unknown	3	12,008	373003	66339	97,392	97,208	N/A	105228	N/A	1,086

Figure S7: Chromatogram of Compound **2** (System H, 300 nm). Purity = 97%.

S3.3 Compound **3**



Peak Information

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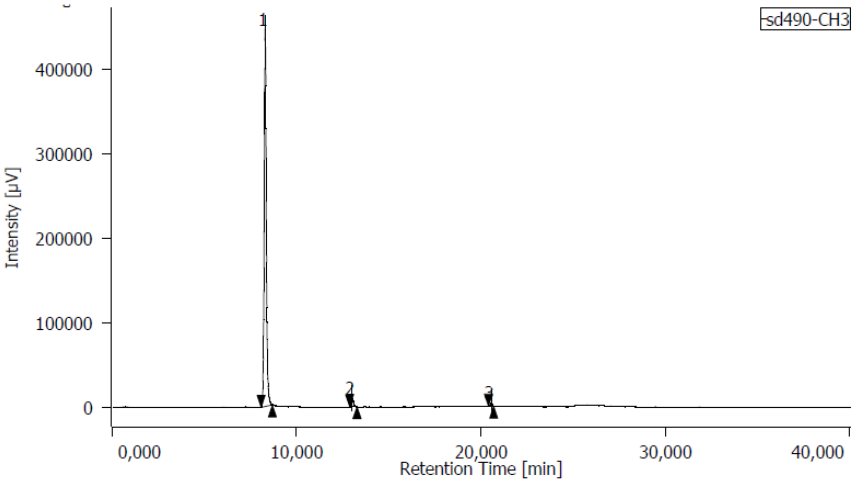
1	Unknown	3	13,375	783954	100262	99,113	99,087	N/A	73638	22,560	1,260
2	Unknown	3	17,875	7016	924	0,887	0,913	N/A	124240	N/A	1,162

Figure S8: Chromatogram of Compound **3** (System I, 300 nm). Purity = 99%.

S3.4 Compound **4**



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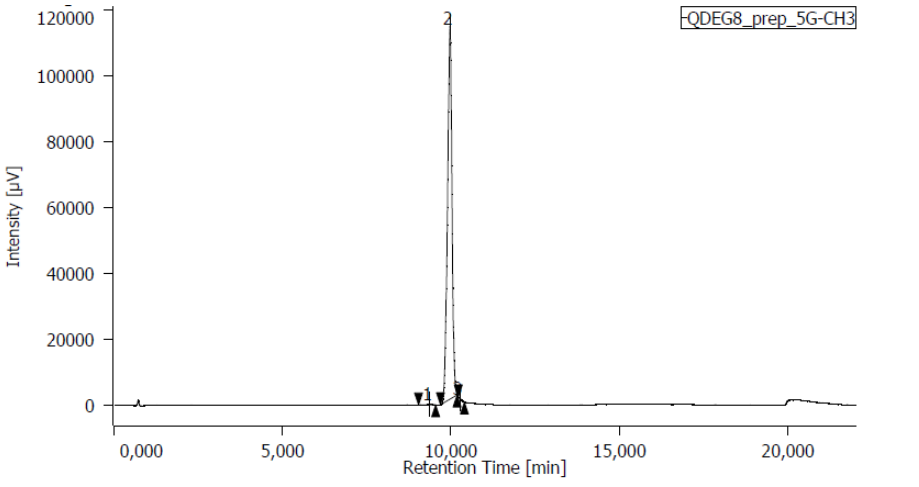
1	Unknown	3	8,308	3590066	448237	96,992	96,933	N/A	27757	22,365	1,105
2	Unknown	3	13,025	85252	9902	2,303	2,141	N/A	54374	39,198	1,220
3	Unknown	3	20,558	26095	4282	0,705	0,926	N/A	257787	N/A	0,947

Figure S9: Chromatogram of Compound **4** (System I, 300 nm). Purity = 97%.

S3.5 Compound **6**



Peak Information

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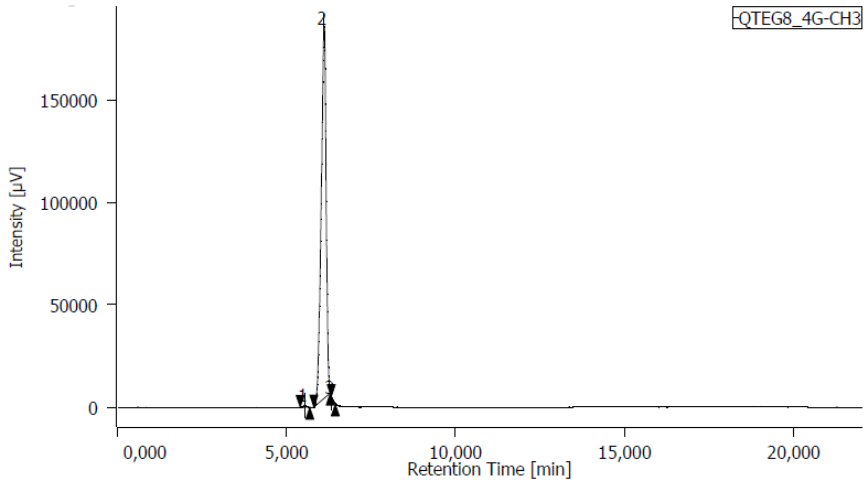
1	Unknown	3	9,367	2829	288	0,270	0,254	N/A	35086	2,784	0,788	
2	Unknown	3	9,975	1045341	113260	99,640	99,740	N/A	28083	1,218	0,912	
3	Unknown	3	10,267	953	8	0,091	0,007	N/A	28733	N/A	6,467	

Figure S10: Chromatogram of Compound **6** (System A, 300 nm). Purity > 99%.

S3.6 Compound **7**

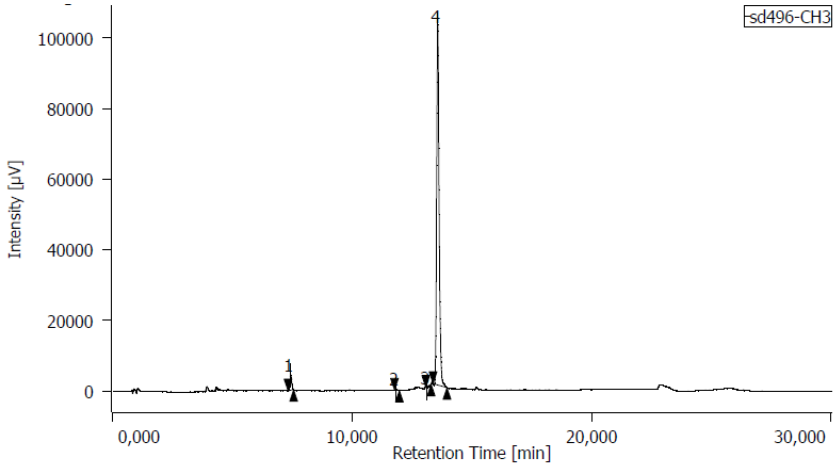


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	5,542	5673	669	0,306	0,368	N/A	8890	2,288	1,071	
2	Unknown	3	6,117	1848873	181143	99,635	99,569	N/A	8285	N/A	0,850	
3	Unknown	3	6,342	1096	115	0,059	0,063	N/A	N/A	N/A	N/A	

Figure S11: Chromatogram of Compound **7** (System B, 300 nm). Purity > 99%.

S3.7 Compound **8**



Peak Information

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1	Unknown	3	7,450	21325	4301	2,847	4,023	N/A	50654	30,868	1,250	
2	Unknown	3	11,850	1290	225	0,172	0,210	N/A	95433	5,329	1,252	
3	Unknown	3	13,133	3523	408	0,470	0,382	N/A	25427	1,772	2,324	
4	Unknown	3	13,583	723013	101960	96,511	95,385	N/A	91439	N/A	1,249	

Figure S12: Chromatogram of Compound **8** (System C, 300 nm). Purity = 96%.

S4 Crystallography

Compound **4** was crystallized from Et_2O. X-ray analysis was carried out at the IECB X-ray facility (UMS 3033 CNRS, INSERM US001, Bordeaux University) on a High flux RIGAKU FRX rotating anode at the Cu Kα wavelength. The diffractometer was equipped with a partial Chi 3 circles goniometer and a hybrid pixel detector DECTRIS PILATUS® 200K 20Hz. The crystal was collected at 130 K and mounted on a cryo-loop after quick soaking on Paratone-N oil from Hampton research before being flash-frozen. The data were processed using the RIGAKU CrystalClear© suite version 2.1 b32.[1] The structure was solved using the charge flipping algorithm implemented in SUPERFLIP [2] and refined using SHELXL-2013 through the integrated WinGX system.[3] The positions of most of the H atoms were determined from fourier difference maps analysis or deduced from coordinates of the non-H atoms and confirmed by Fourier synthesis. H atoms were included for structure factor calculations and their positions refined for some of them (see cif file). The non-H atoms were refined with anisotropic temperature parameters.

Data statistics are shown in Table S5.

Name	Compound 4
CCDC number	1056802
Formula	$C_{34}H_{36}N_2O_8S$
M	632.71
Crystal system	Monoclinic
Space group	C2/c
a/Å	36.453(3)
b/Å	9.0477(6)
c/Å	19.1022(13)
U/Å^3	6137.8(7)
T/K	130(2)
Z	8
ρg cm^{-1}	1.369
Size (mm)	0.2 x 0.1 x 0.01
λÅ	1.5418
μ/mm^{-1}	1.373
Unique data	5837
Parameters/Restraints	413/0
Final R indices [I>2sigma(I)]	R1 = 0.0509, wR2 = 0.1167
Goodness of fit	1.058

Table S5: X-ray crystallographic data.

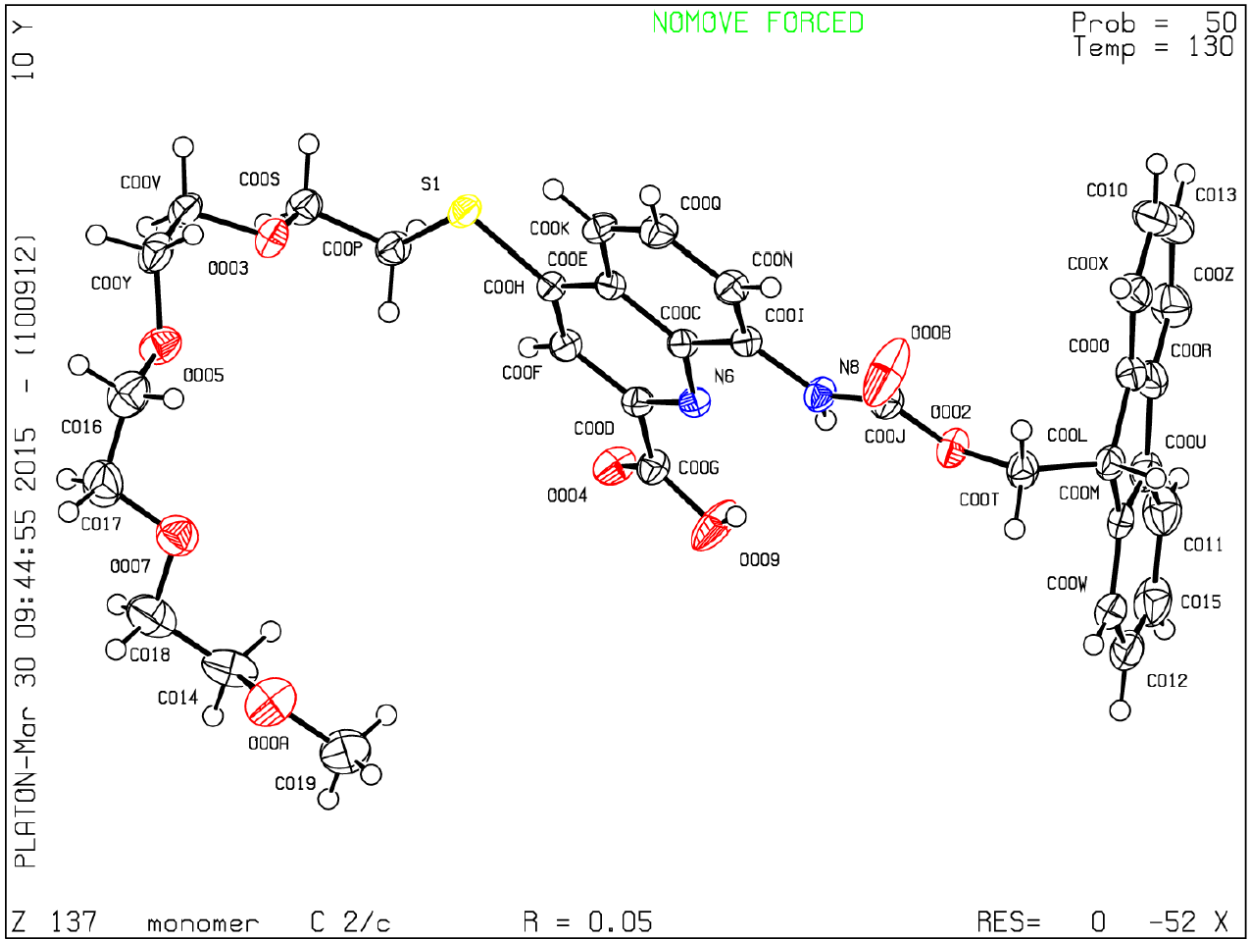
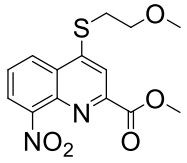
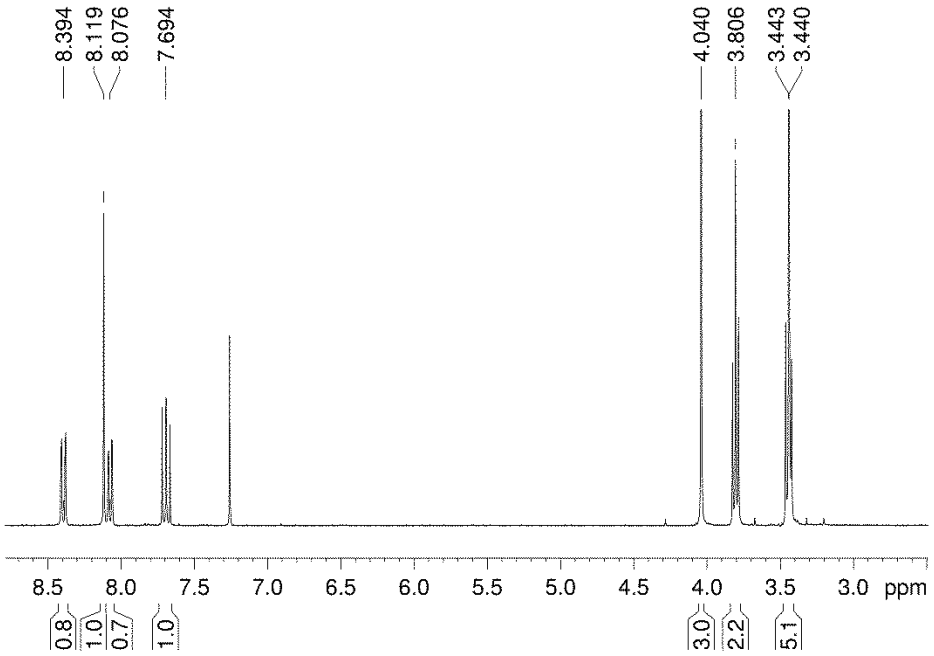
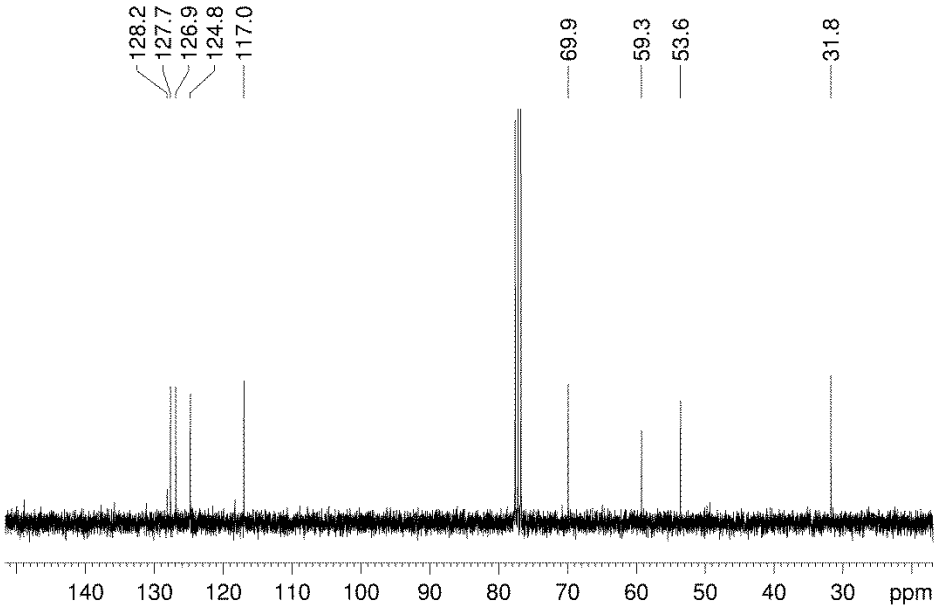


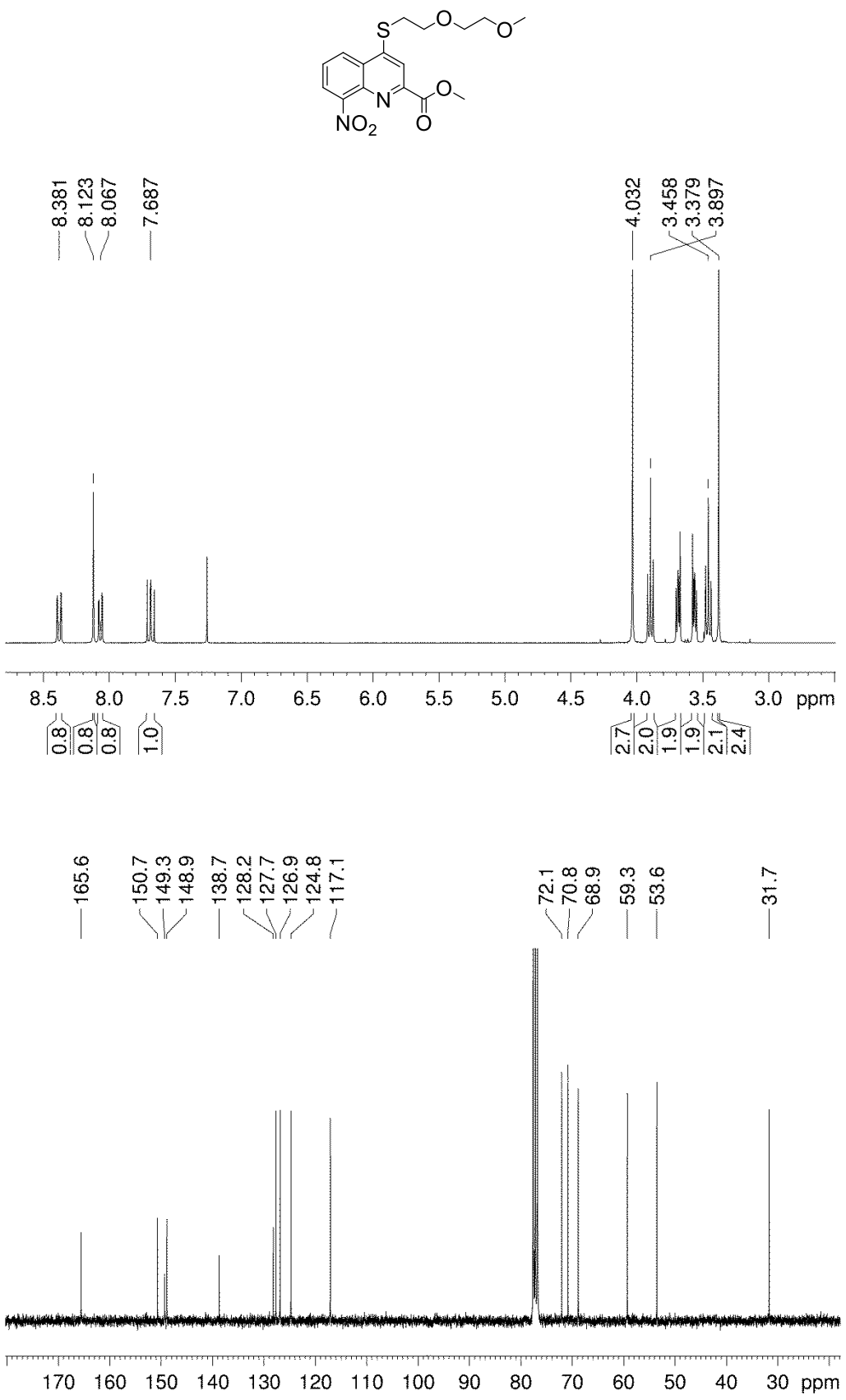
Figure S13: Crystal structure of monomer 4.

S5 NMR spectra





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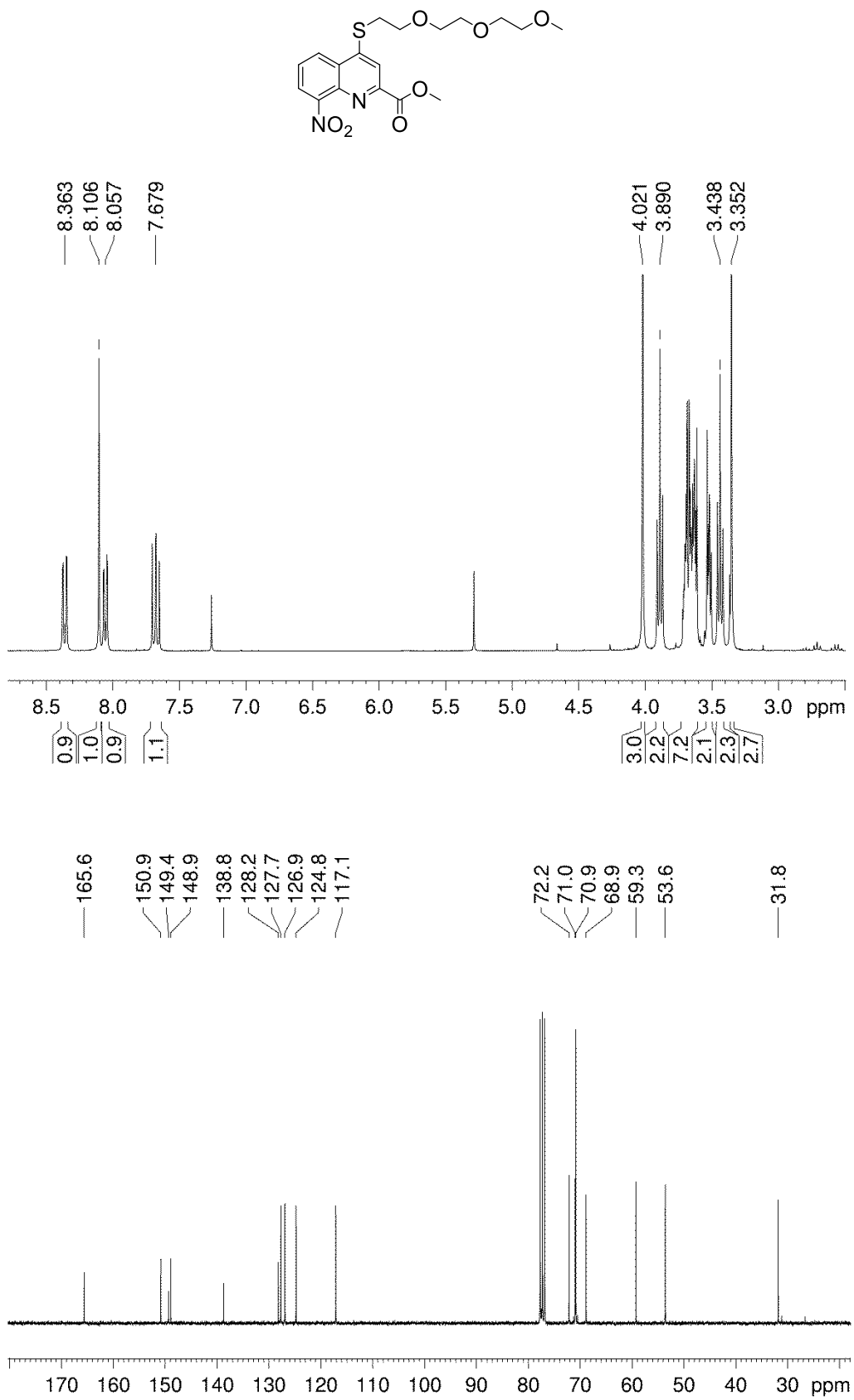
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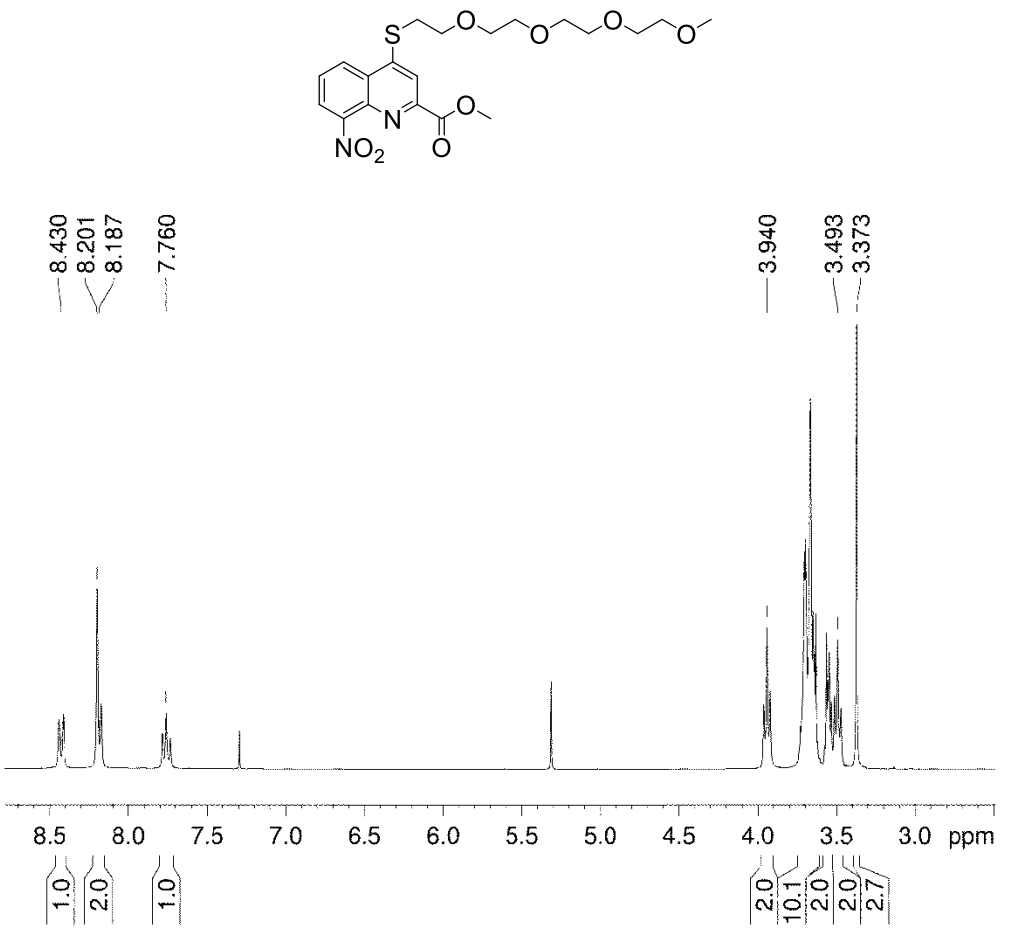
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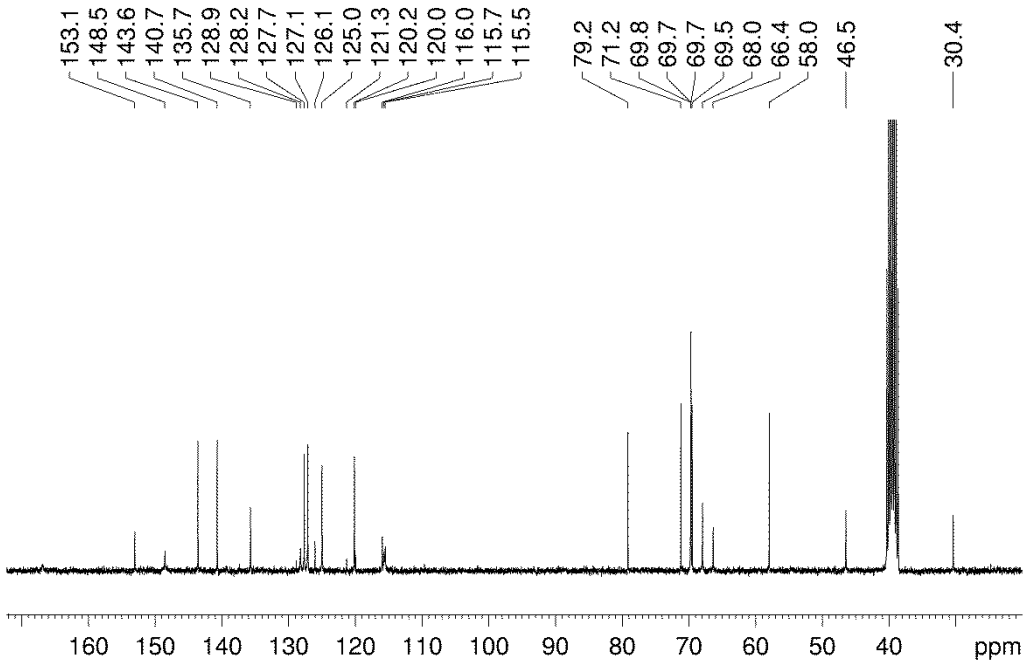
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69.5
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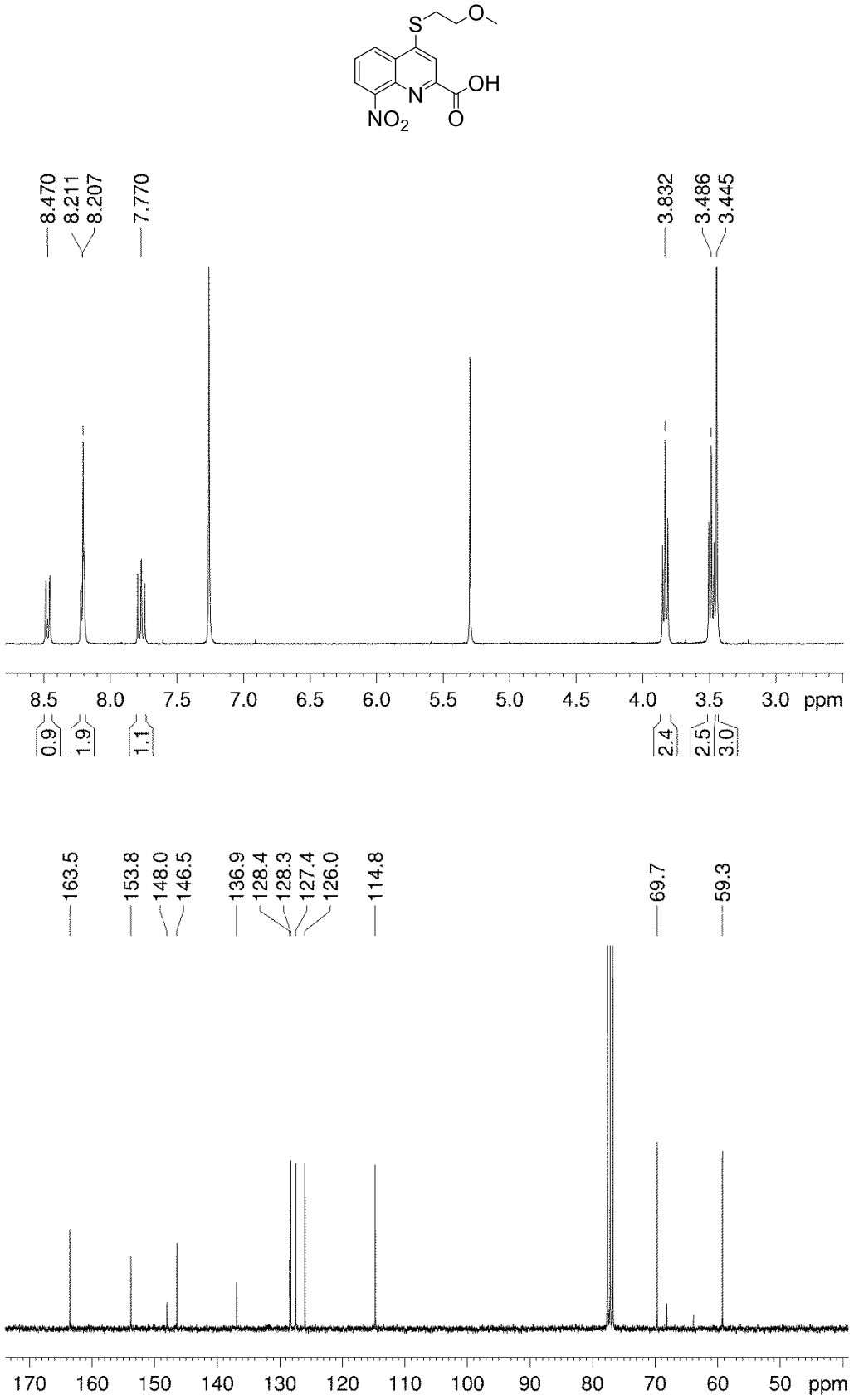
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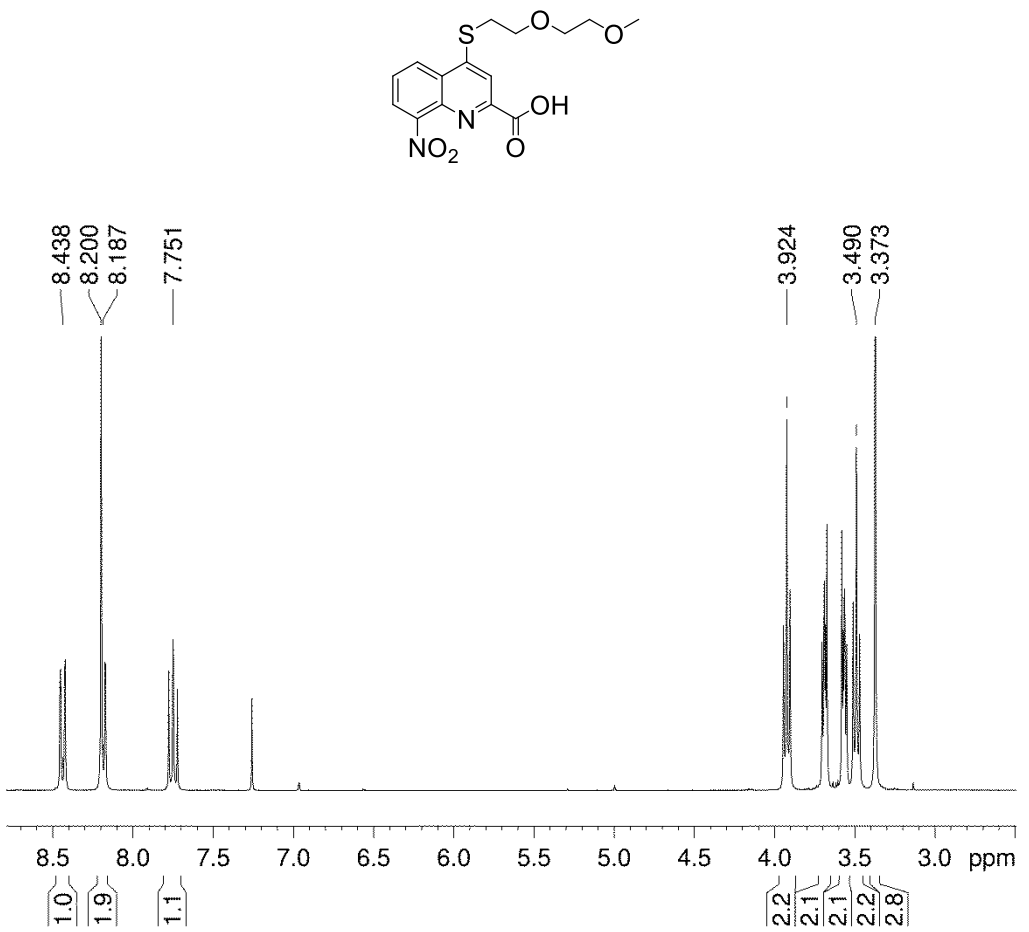
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2.2
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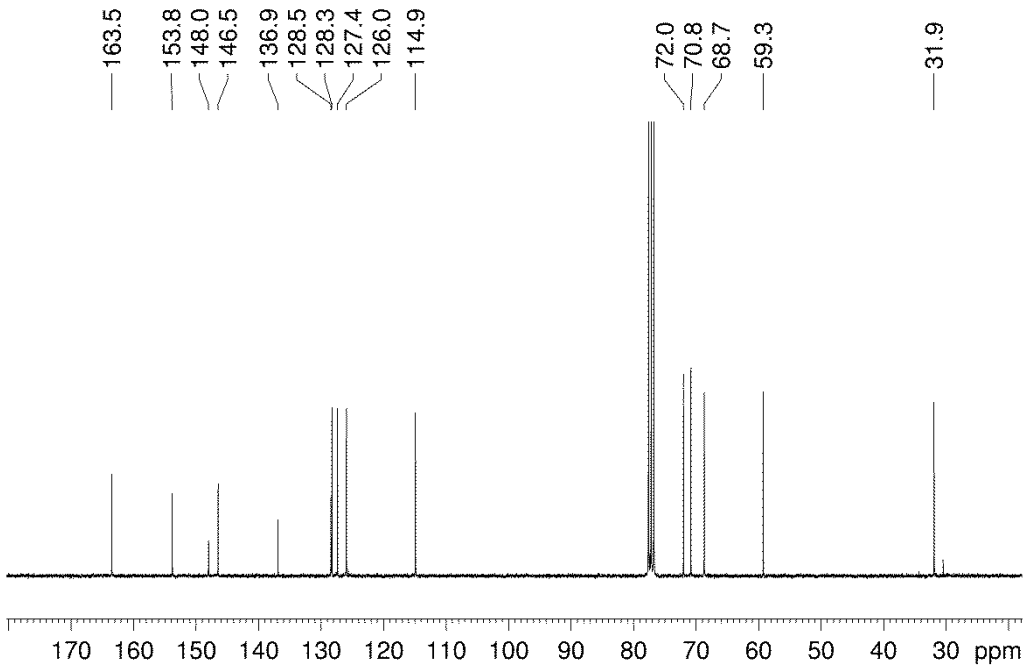
2.1
2.2
2.8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128.3
127.4
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114.9
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150
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130
120
110
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90
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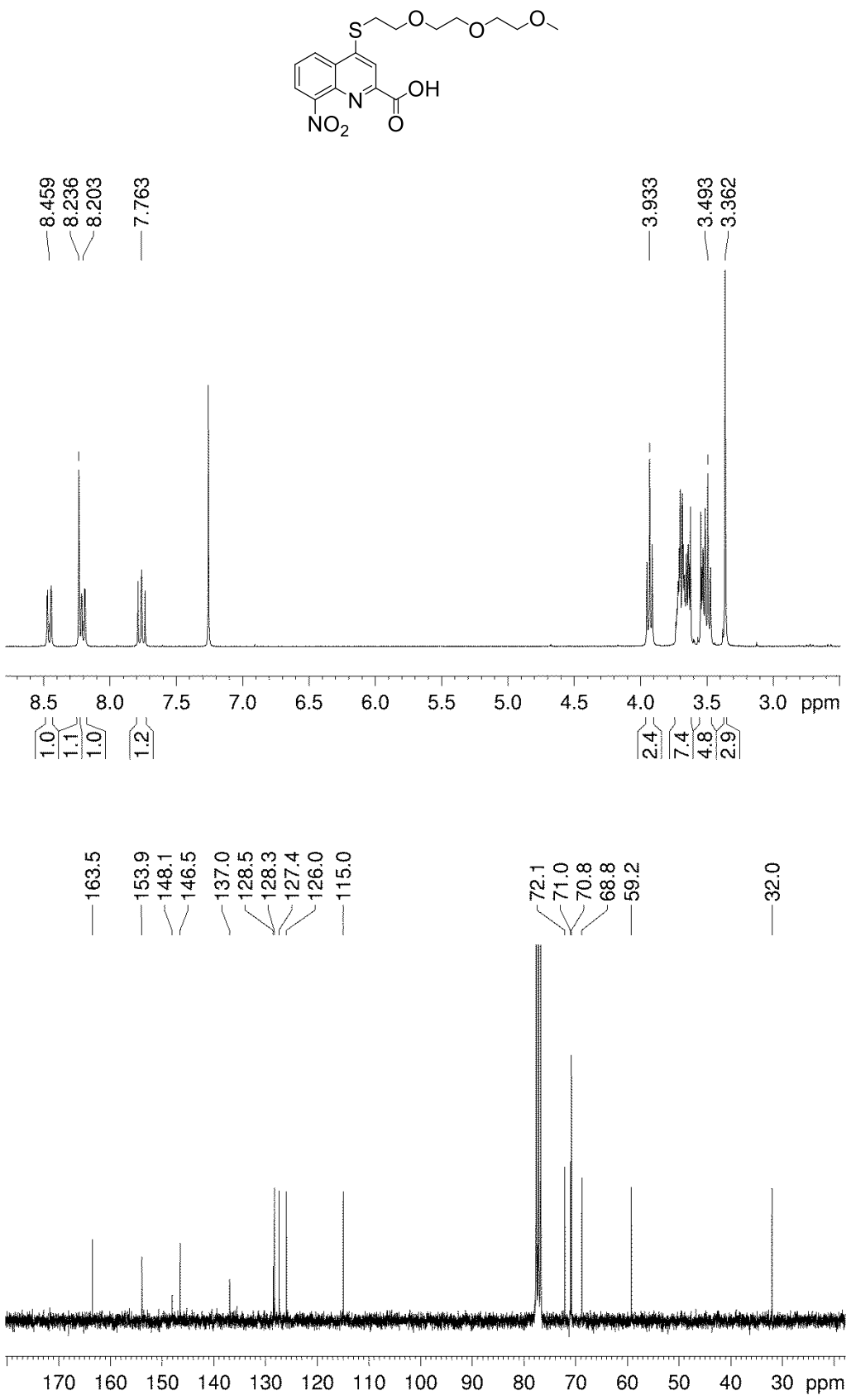
50
40
30
ppm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O
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OH
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O
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7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
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1.1
1.0
1.2
2.4
7.4
4.8
2.9
163.5
153.9
148.1
146.5
137.0
128.5
128.3
127.4
126.0
115.0
72.1
71.0
70.8
68.8
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150
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130
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110
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90
80
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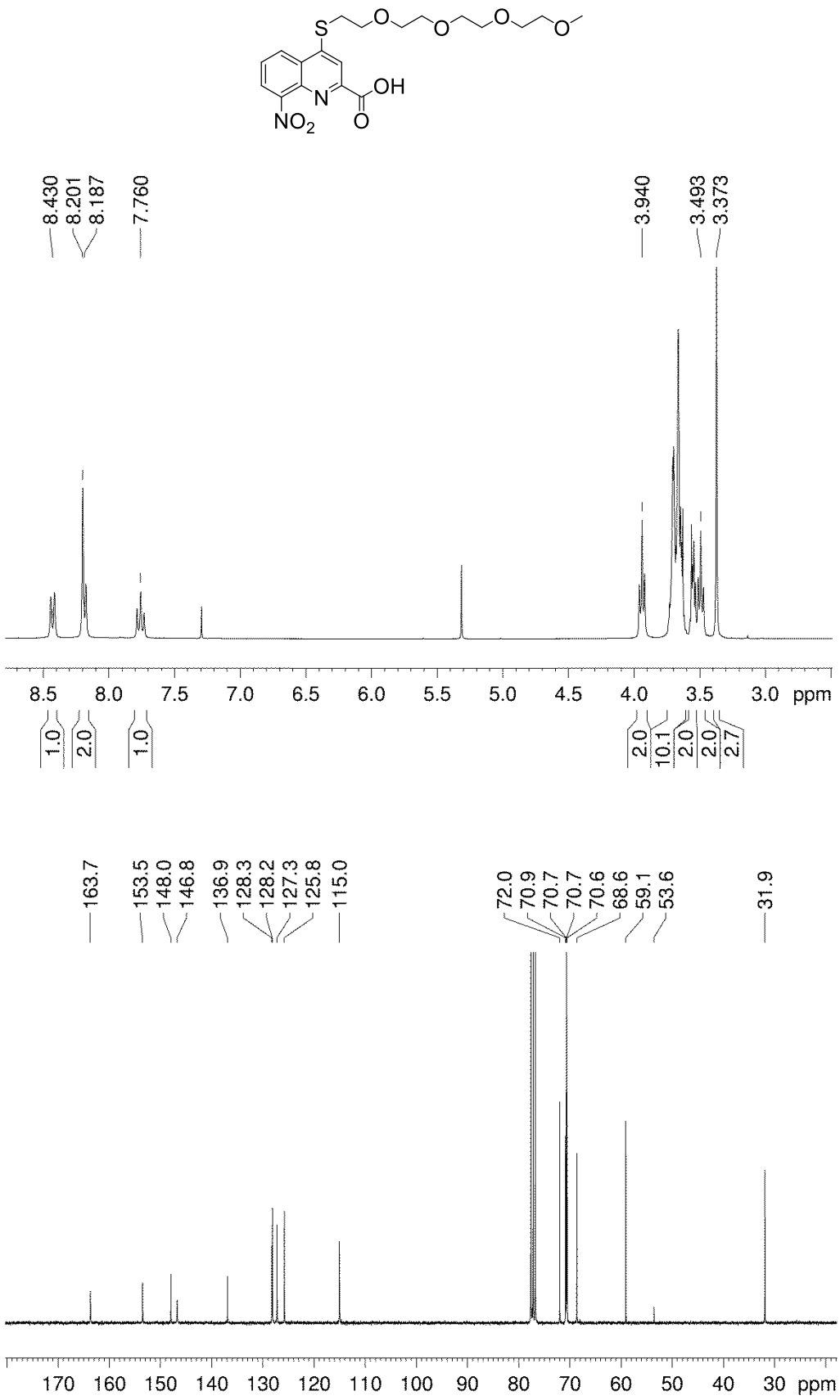
60
50
40
30
ppm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O
O
O
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O
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8.187
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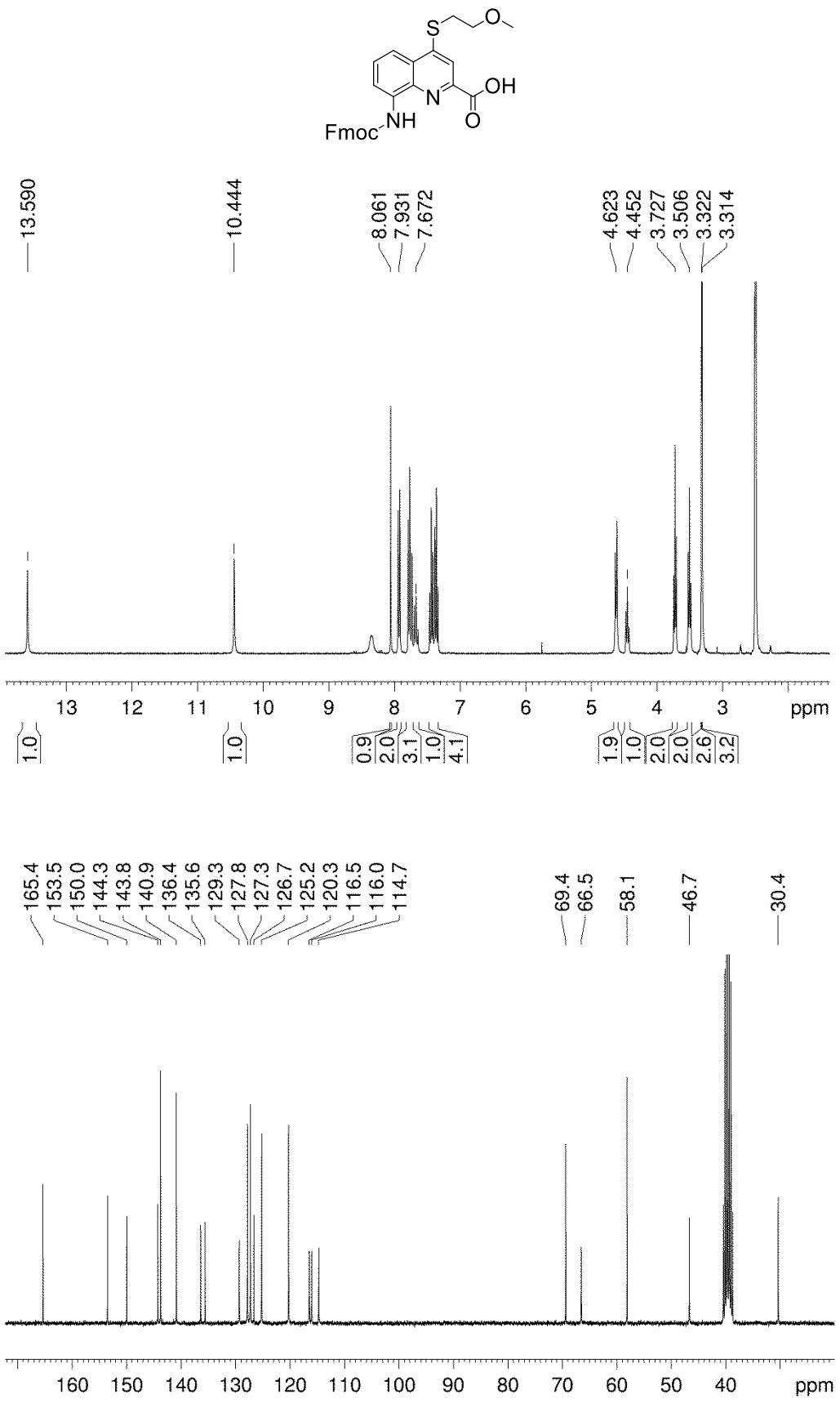
3.373
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
1.0
2.0
1.0
2.0
10.1
2.0
2.0
2.7
163.7
153.5
148.0
146.8
136.9
128.3
128.2
127.3
125.8
115.0
72.0
70.9
70.7
70.7
70.6
68.6
59.1
53.6
31.9
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm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3.727
3.506
3.322
3.314
ppm
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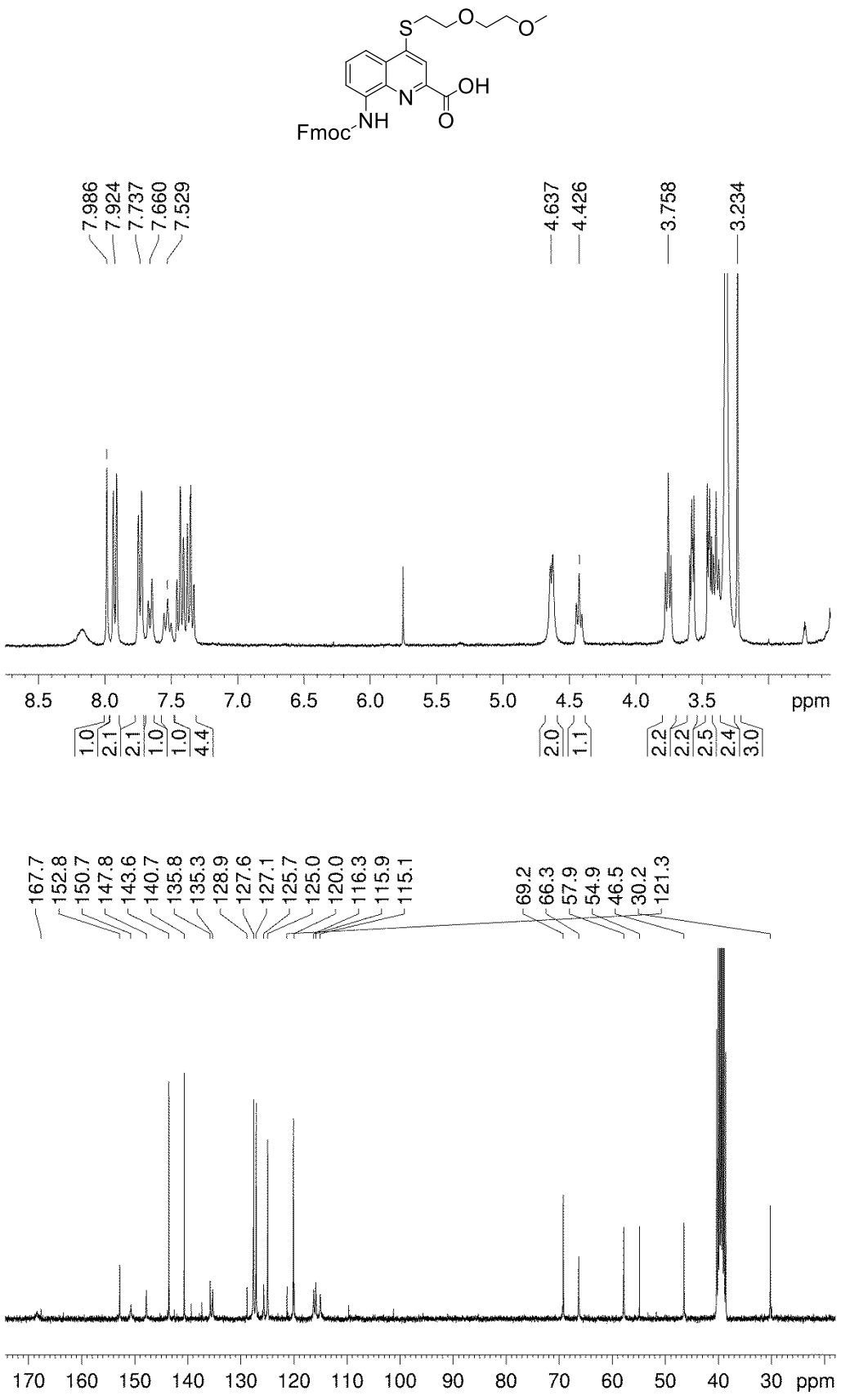
153.5
150.0
144.3
143.8
140.9
136.4
135.6
129.3
127.8
127.3
126.7
125.2
120.3
116.5
116.0
114.7
69.4
66.5
58.1
46.7
30.4
ppm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O
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N
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O
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7.924
7.737
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3.758
3.234
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
1.0
2.1
2.1
1.0
1.0
4.4
2.0
1.1
2.2
2.2
2.5
2.4
3.0
167.7
152.8
150.7
147.8
143.6
140.7
135.8
135.3
128.9
127.6
127.1
125.7
125.0
120.0
116.3
115.9
115.1
69.2
66.3
57.9
54.9
46.5
30.2
121.3
170
160
150
140
130
120
110
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90
80
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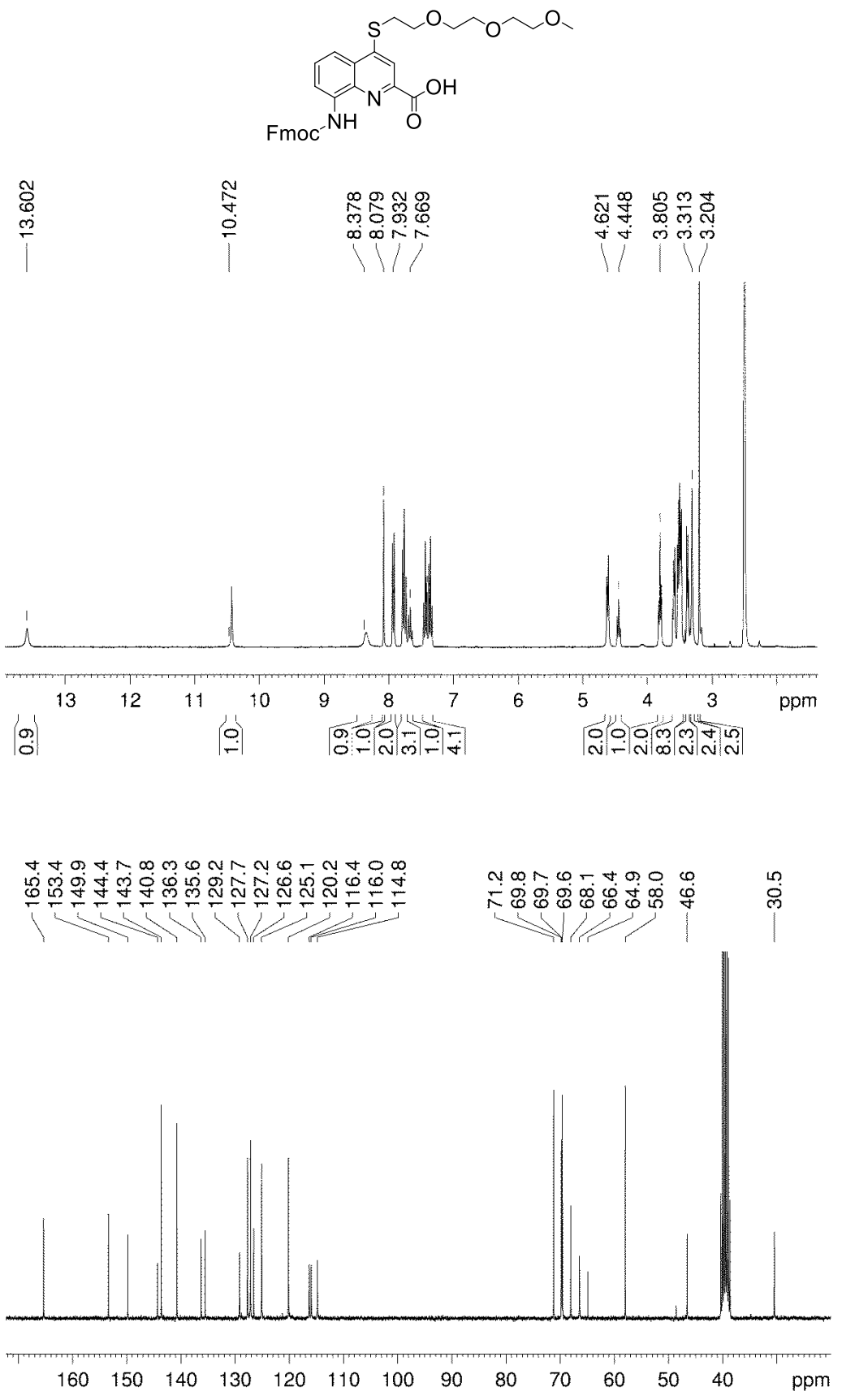
60
50
40
30
ppm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NH
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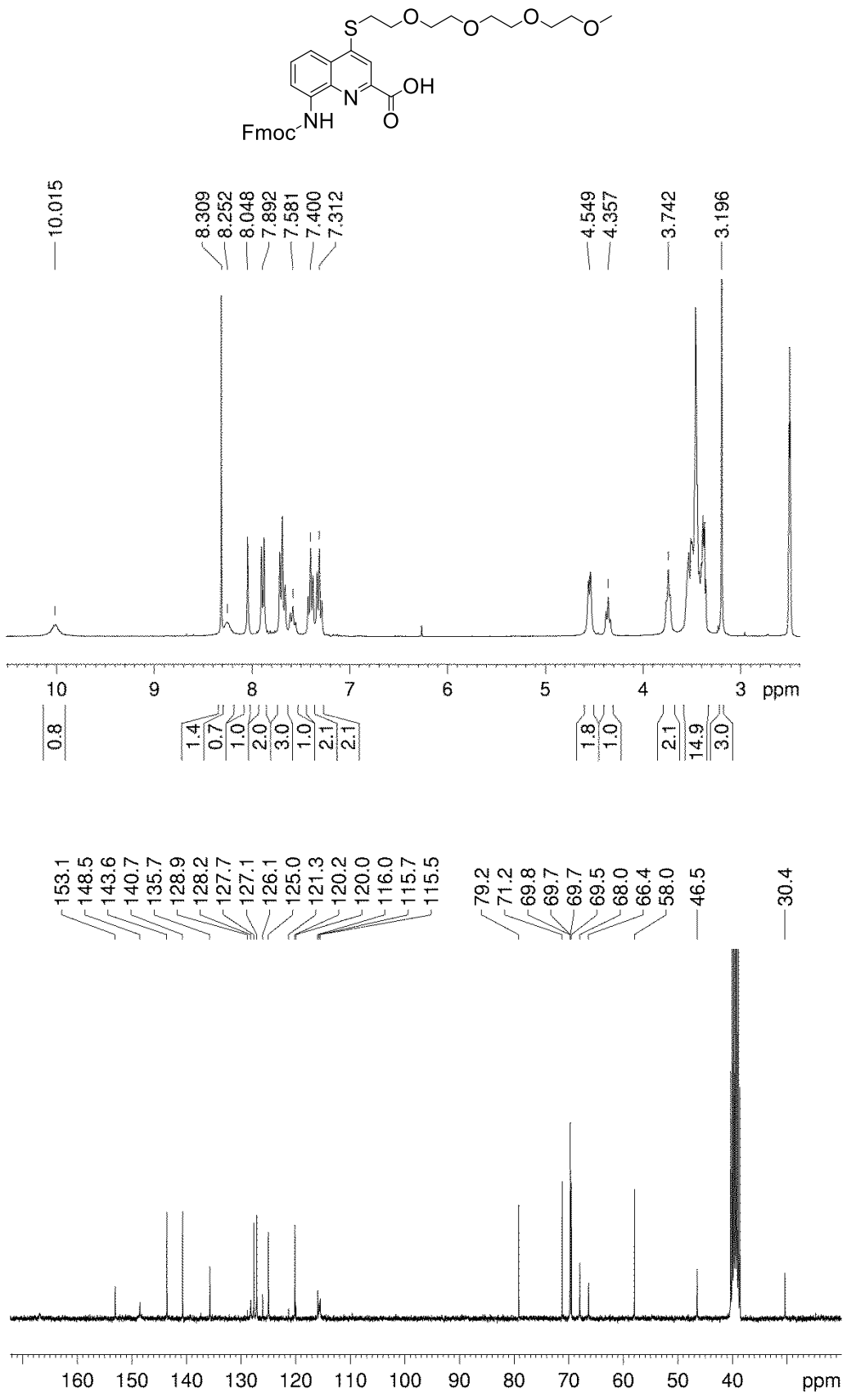
4.621
4.448
3.805
3.313
3.204
ppm
165.4
153.4
149.9
144.4
143.7
140.8
136.3
135.6
129.2
127.7
127.2
126.6
125.1
120.2
116.4
116.0
114.8
71.2
69.8
69.7
69.6
68.1
66.4
64.9
58.0
46.6
30.5
ppm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O
O
O
O
OH
N
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NH
Fmoc
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8.048
7.892
7.581
7.400
7.312
4.549
4.357
3.742
3.196
10
9
8
7
6
5
4
3
ppm
0.8
1.4
0.7
1.0
2.0
3.0
1.0
2.1
2.1
1.8
1.0
2.1
14.9
3.0
153.1
148.5
143.6
140.7
135.7
128.9
128.2
127.7
127.1
126.1
125.0
121.3
120.2
120.0
116.0
115.7
115.5
79.2
71.2
69.8
69.7
69.7
69.5
68.0
66.4
58.0
46.5
30.4
160
150
140
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120
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100
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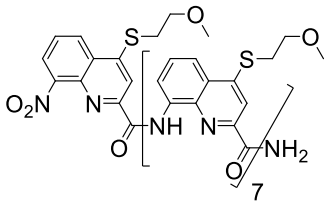
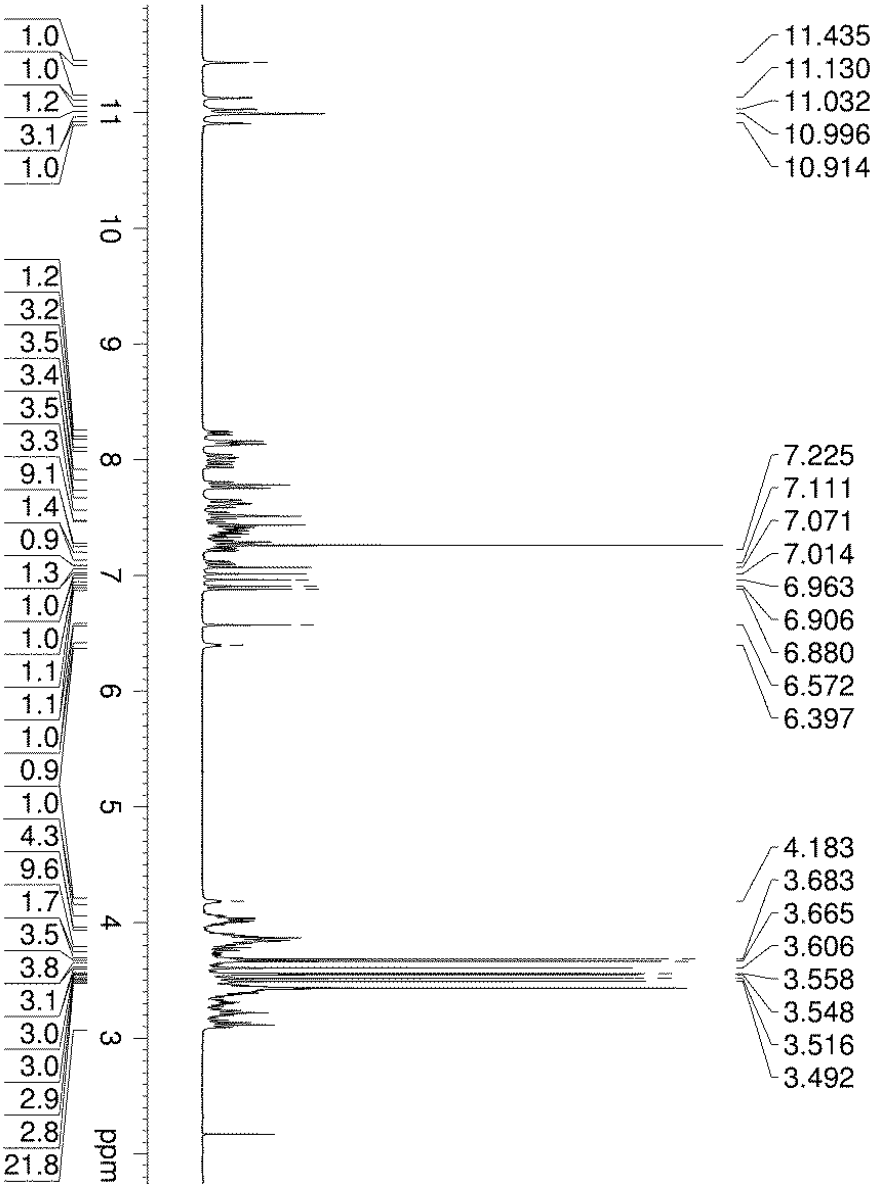
60
50
40
ppm


O
S
O
S
O_2N
N
NH
N
O
NH_2
O
7


1.0
1.0
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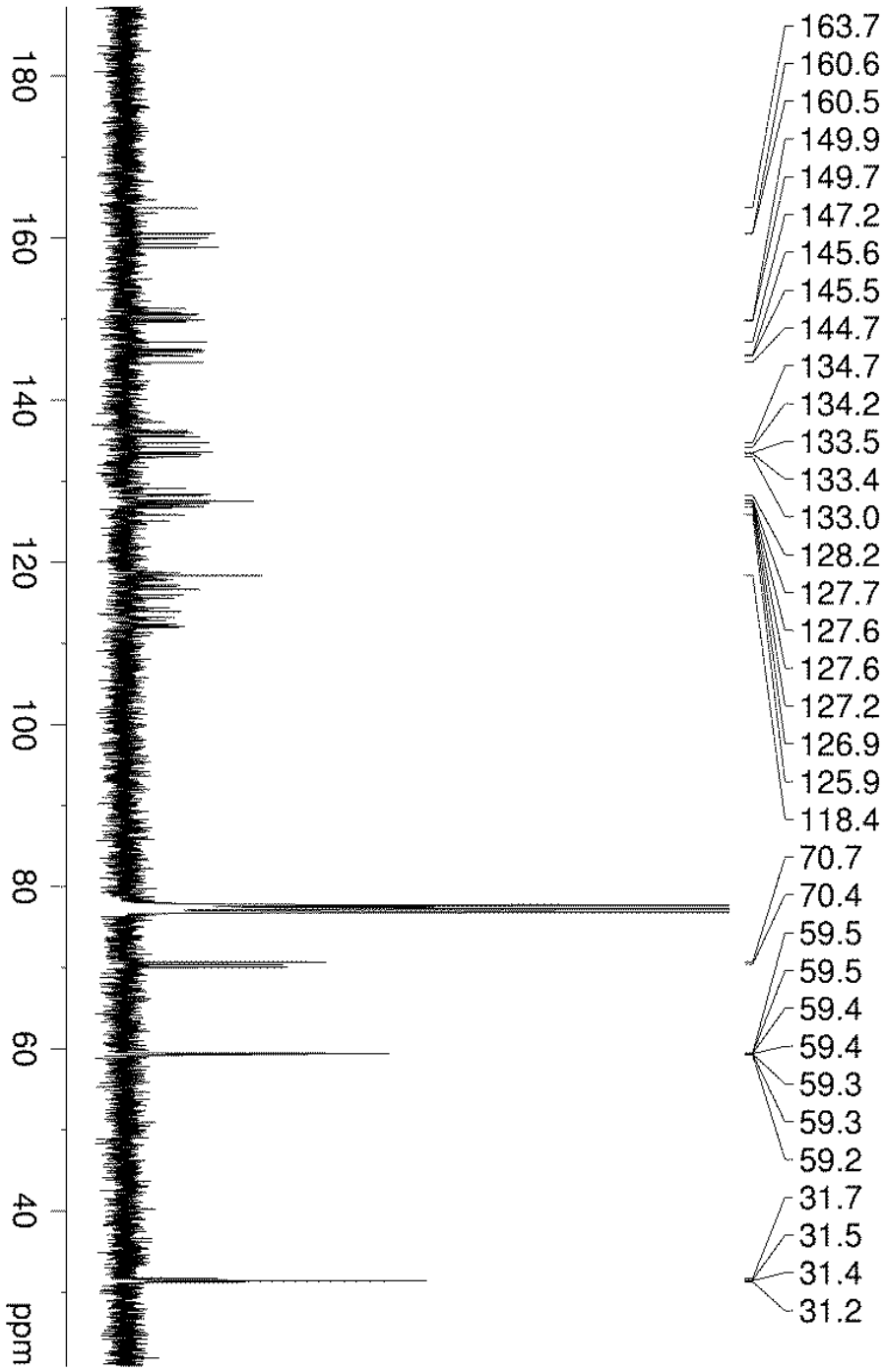
1.0
1.2
3.2
3.5
3.4
3.5
3.3
9.1
1.4
0.9
1.3
1.0
1.0
1.1
1.1
1.0
0.9
1.0
4.3
9.6
1.7
3.5
3.8
3.1
3.0
3.0
2.9
2.8
21.8
ppm
11
10
9
8
7
6
5
4
3
11.435
11.130
11.032
10.996
10.914
7.225
7.111
7.071
7.014
6.963
6.906
6.880
6.572
6.397
4.183
3.683
3.665
3.606
3.558
3.548
3.516
3.492


180
160
140
120
100
80
60
40
ppm
163.7
160.6
160.5
149.9
149.7
147.2
145.6
145.5
144.7
134.7
134.2
133.5
133.4
133.0
128.2
127.7
127.6
127.6
127.2
126.9
125.9
118.4
70.7
70.4
59.5
59.5
59.4
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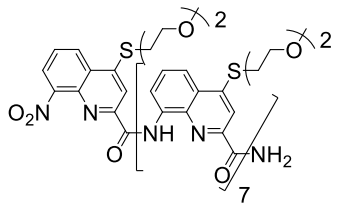
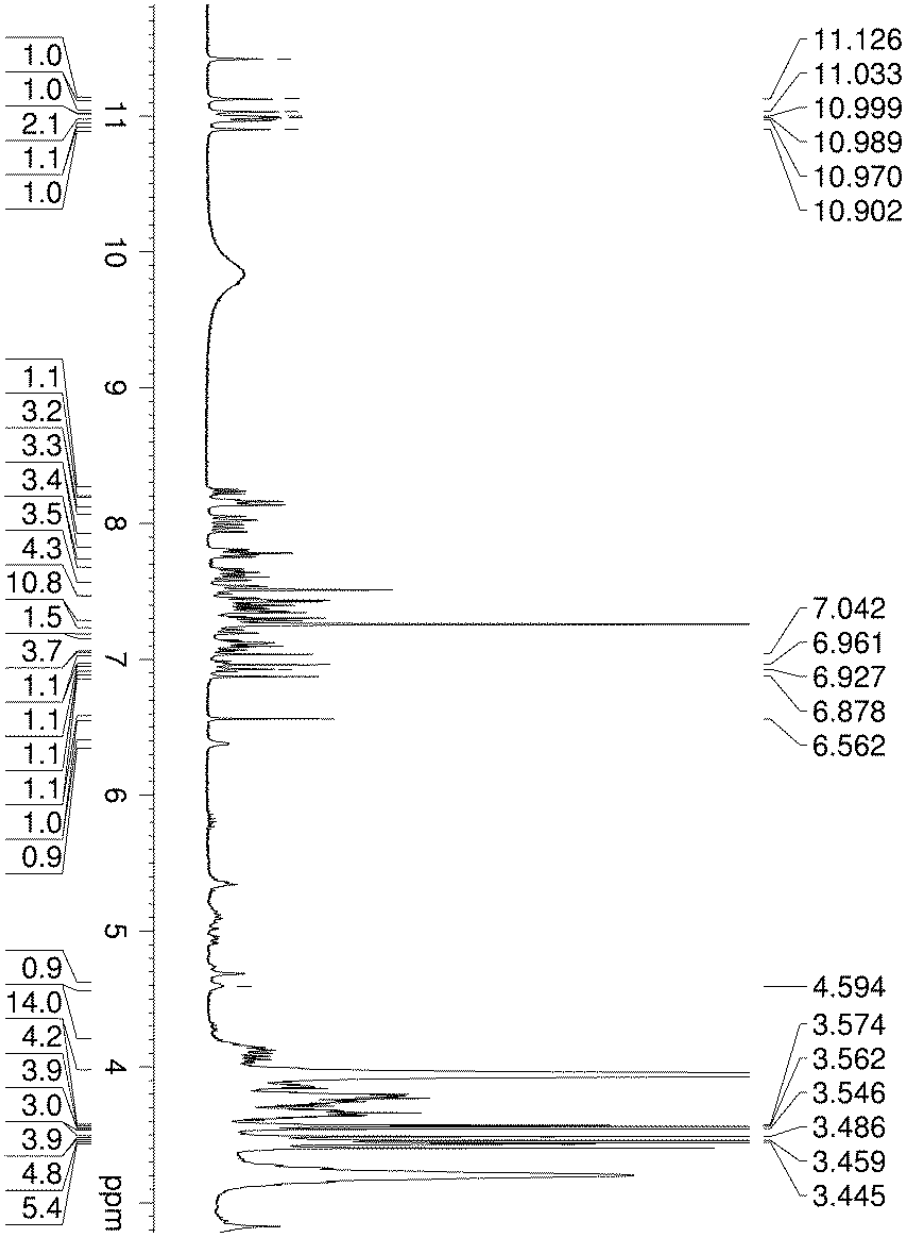
59.3
59.2
31.7
31.5
31.4
31.2


O2N
N
S
O
NH
N
S
O
NH2
O
2
2
7


1.0
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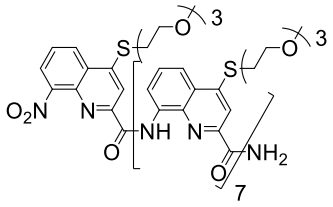
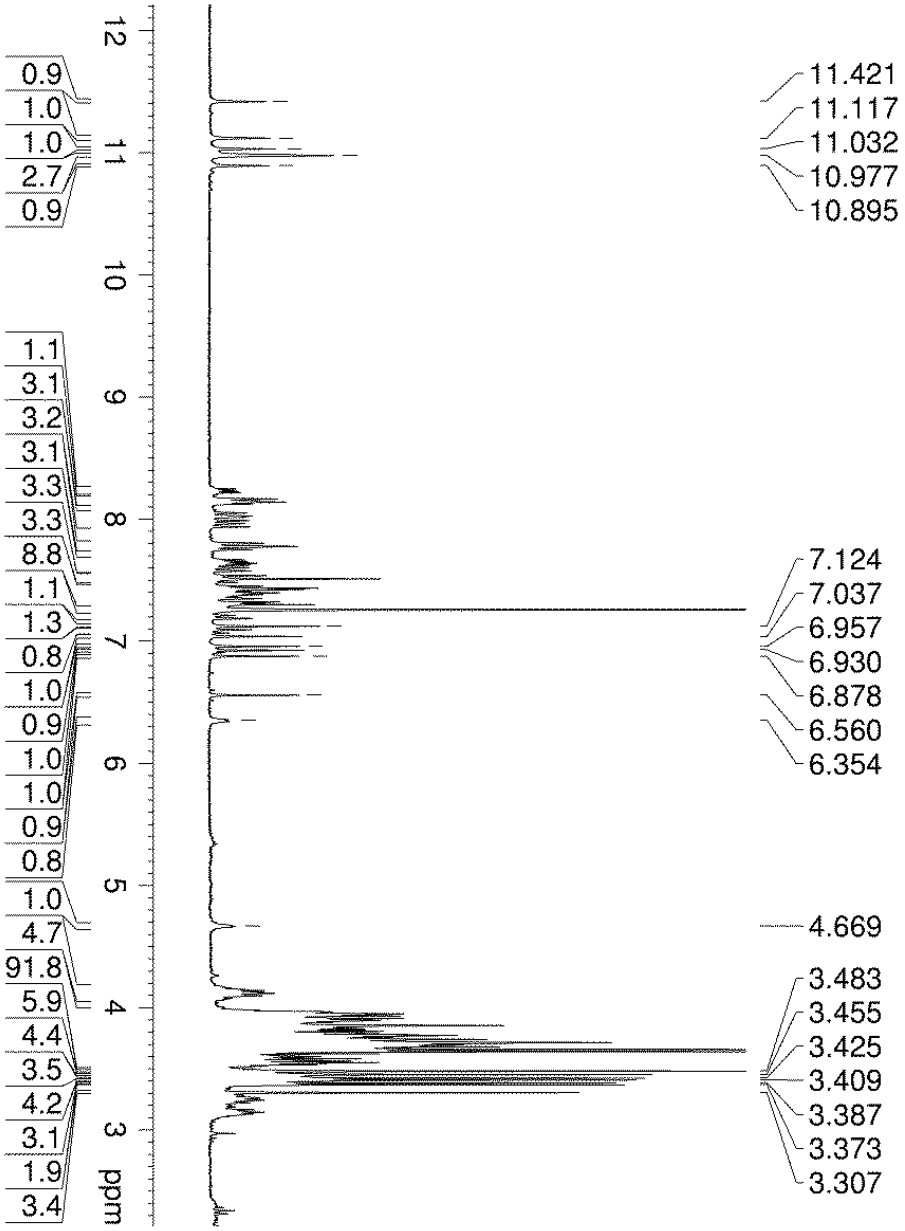
1.0
1.1
3.2
3.3
3.4
3.5
4.3
10.8
1.5
3.7
1.1
1.1
1.1
1.1
1.0
0.9
0.9
14.0
4.2
3.9
3.0
3.9
4.8
5.4
11
10
9
8
7
6
5
4
ppm
11.126
11.033
10.999
10.989
10.970
10.902
7.042
6.961
6.927
6.878
6.562
4.594
3.574
3.562
3.546
3.486
3.459
3.445


O2N
N
NH
N
O
S
O
3
NH2
7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4.669
3.483
3.455
3.425
3.409
3.387
3.373
3.307
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1.0
1.0
2.7
0.9
1.1
3.1
3.2
3.1
3.3
3.3
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1.1
1.3
0.8
1.0
0.9
1.0
1.0
0.9
0.8
1.0
4.7
91.8
5.9
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3.1
1.9
3.4
12
11
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9
8
7
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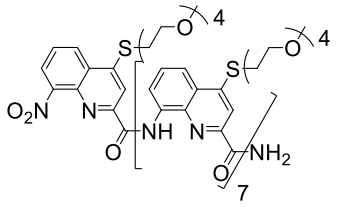
5
4
3
ppm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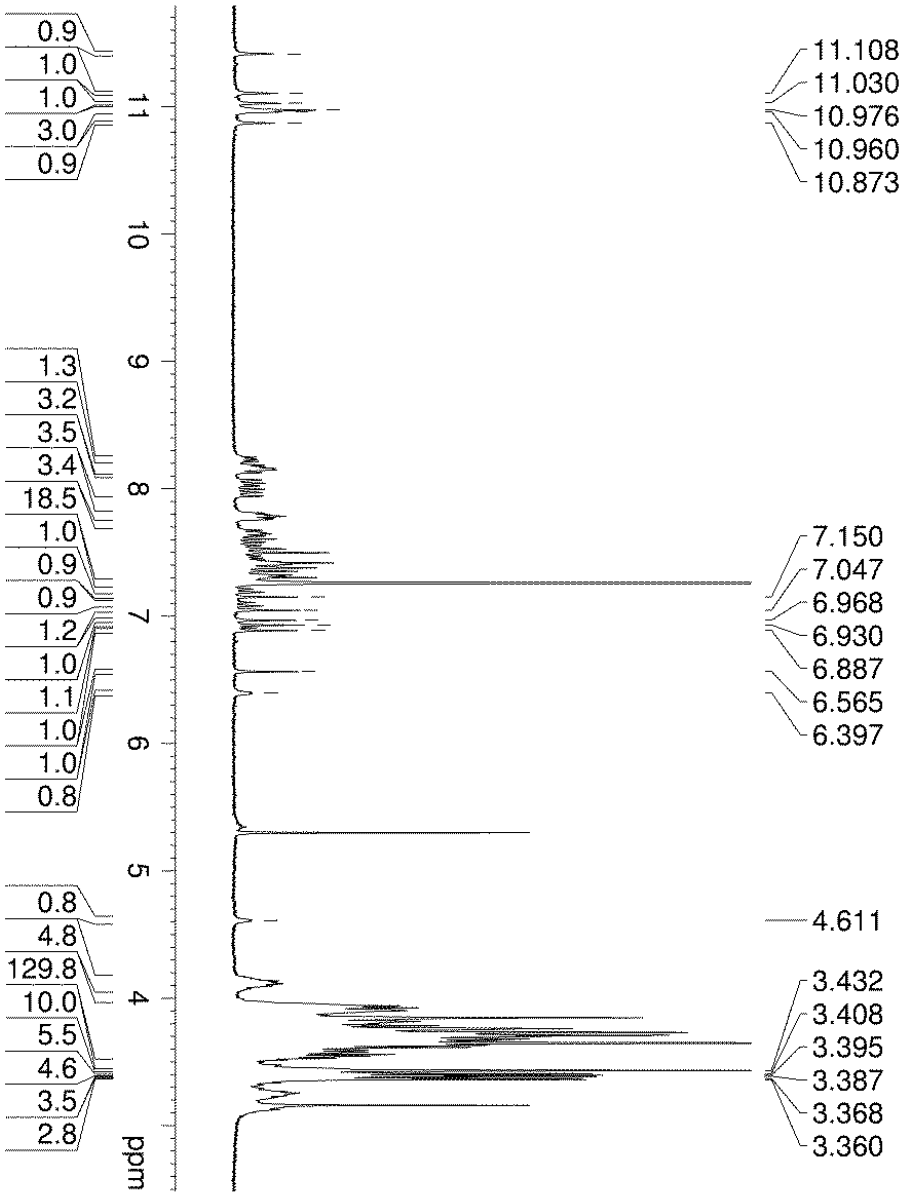
NH
N
O
S
O
4
NH2
7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0.9
1.2
1.0
1.1
1.0
1.0
0.8
0.8
4.8
129.8
10.0
5.5
4.6
3.5
2.8
11.108
11.030
10.976
10.960
10.873
7.150
7.047
6.968
6.930
6.887
6.565
6.397
4.611
3.432
3.408
3.395
3.387
3.368
3.360
ppm

S6 References

[1] CrystalClear (Version 2.1). MSC, The Woodlands, Texas, USA.

[2] L. Palatinus, G. Chapuis. J. Appl. Cryst. 2007, 40, 786.

[3] L. J. Farrugia, J. Appl. Cryst. 2012, 45, 849.